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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/898,809	07/03/2001	Raghavan Rajagopalan	MRD/63	5120
26875	7590	02/09/2005	EXAMINER	
WOOD, HERRON & EVANS, LLP 2700 CAREW TOWER 441 VINE STREET CINCINNATI, OH 45202			MCKENZIE, THOMAS C	
			ART UNIT	PAPER NUMBER
			1624	

DATE MAILED: 02/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/898,809

Applicant(s)

RAJAGOPALAN ET AL.

Examiner

Thomas McKenzie, Ph.D.

Art Unit

1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 March 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 12-14 and 23-33 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 12-14 and 23-33 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 03 July 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>2</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. This action is in response to amendments filed on 8/20/04 and 1/27/05 as well as a RCE filed on 11/19/04. Applicant has amended claims 12, 14, 23, 32, and 33. Applicant has canceled claim 12. There are no new claims. Claims 12-14 and 23-33 were previously rejected. This is the seventh action on the merits. The application concerns some uses of cyanine dye compositions.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on 8/20/04 and on 1/27/05 have been entered.

Response to Amendment

3. Applicants' amendment of 8/20/04, requiring E to be a radical overcomes the indefiniteness rejection made in point #3 of the Final rejection of 5/21/04. Applicants' amendment replacing "phototherapeutic procedure" by "photo procedure" overcomes the enablement rejections made in point #9 and the written description rejection made in point #10 of that action. Applicants are no longer claiming therapy.

4. The declaration by Dr. Rajajoplan under 37 CFR 1.132 filed 1/24/05 is insufficient to overcome the rejection of claims 12-14, 23-31, and 33 based upon indefiniteness, lack of enablement, and lack of written description as set forth in points #4, #5, #7, and #8 the last Office action because: the references cited fail to make clear that the structures of all these functionally defined radicals are well enough known to "permit one skilled in the art to immediately envisage the product claimed" as required by MPEP §2161 I. A. None of these references supply the "known or disclosed correlation between function and structure" required by MPEP §2161 II. A. 2 (a). The references merely cite examples of compounds fitting Applicants' functional definition. What is required is the structures of all molecules fitting these functional limitations. The enablement, written description, and definiteness of terms must be as of Applicants' effective filing date of 2000. For example, Nunn (European J. Pharmacology.) is dated 3 years after that date and provides only 3 compounds that bind to one subtype of somatostatin receptor. Bass (Molecular Pharmacology), dated 1996, discloses 6 compounds that bind to four different somatostatin subtypes. Are Applicants' claims to radicals derived from somatostatin binding molecules limited to these 9 compounds? Are any other radicals being claimed? If so what are their structures. Neither of these two articles makes a definitive structure-activity relationship, so the structures of all

molecules binding to the somatostatin receptor which would be **immediately** (emphasis added) pictured by the skilled chemist as required by the MPEP. The word immediately means that no experimentation or trial and error search will suffice to provide the structure of such molecules.

In this case a separate issue has been raised concerning carbohydrate receptor binding molecules because of the vast number and diversity of such receptors. Applicants offer two papers related to such binding molecules. Mazik (Tetrahedron Letters), dated 2004, 4 years after Applicants effective filing date, reports on the synthesis of artificial carbohydrate binding receptors. The artificial receptors reported in Mazik (Tetrahedron Letters) do not occur in the tissues, which is one of Applicants' claim limitations. The relevance of Mazik (Tetrahedron Letters) to the claim limitation under discussion is, frankly, unknown. Kaila (Med. Chem. Reviews), dated 2002, 2 years after Applicants filing date reports on the binding of one tetra-saccharide (Silyl-X) to two different selectin receptors. No additional molecules binding to E-selectin and P-selectin are taught in this reference. Is Applicants claim limitation a "univalent radical selected from ... carbohydrate receptor binding molecules" limited to Silyl X only? If not, where in this article is the information found that would allow the skilled chemist to

"**immediately** envisage" all such molecules binding to all such carbohydrate receptors?

Also found in MPEP §2161 II A 2 (a) is the requirement that "[a]n adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described.").

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12-14, 23-31, and 33 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrases “somatostatin receptor binding molecule” ... “carbohydrate receptor binding molecule” are all indefinite. What are the chemical structures of these fragments that define radical “E”? These are not art-recognized structural terms. The passage spanning line 17, page 12 to line 12, page 13 lists the function that these radicals are to perform, but does not clarify the molecular structures intended. Applicants’ statement that “E” is an epitope only further clouds the issue. The Examiner understands that an epitope is a portion of a macromolecule chain capable of forming an antibody. Is “E” an antibody or only a short peptide segment from an antibody? If only macromolecules can be epitopes, then how can steroid hormones and amino acids be epitopes? Are the synthetic biomolecules listed in lines 11-13, page 13 “E”?

Nowhere do Applicants provide any assays that could be used to determine such binding. Nowhere do Applicants state how strong the affinity of a molecule for each of these receptors must be for the molecule to fall within the claim limitations. Since the binding affinities of molecules for receptors are dependent

upon the conditions of the assay such information is crucial for determining which molecules are embraced by Applicants' claims.

6. Claims 12-14, 23-31, and 33 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The specific phrase "carbohydrate receptor-binding molecule" is indefinite. There is an entire class of such carbohydrate receptors, quite possibly thousands, and generally poorly understood and characterized. How would one know if any molecule E bound to such a receptor without checking all such receptors?

Applicants argue that

7. Claim 32 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase, "E is a univalent radical that is recognized by and binds to a target site on the tissue" is indefinite. What is the structure of this radical? What targets and which tissues are intended?

Applicants argue that

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-14 and 23-33 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for preparing compounds with radical “E” being dihydroxyindolecarboxylic acid or the peptide Cytate, does not reasonably provide enablement for preparing all the other functionally described E binding molecules. The specification does not enable any person skilled in the art of organic synthesis to make the invention commensurate in scope with these claims.

“The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims.” *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. The issue is synthesizing compounds whose structures are not known.

a) If E is an epitope from an antibody, raising all possible antibodies to the somatostatin receptor and locating all the possible epitope sites on these antibodies is an impossible task. Alternatively, screening all “hormones, amino acids, peptides, ... and aptamers” to determine if they bind to the receptors listed in claim

1 is an open-ended and potentially inconclusive research project. Locating the epitope on any particular antibody to a somatostatin receptor say, would a moderate degree of experimentation. However, all possible antibodies would have to be made because the individual epitope sites would differ. After this is done, each individual radical would have to be synthesized in a form that would allow attachment to the rest of the pictured molecule. Thus, the quantity of experimentation required is huge. b) The direction concerning the compounds claimed is found in Figure 2. In that figure, the radical "E" is described as "Biomolecule". Thus, Figure 2 does not appear to be a working example. There is neither direction given concerning the synthesis of "biomolecule" nor its attachment to the rest of the claimed formula. c) There are no working examples of a compound of formula given in claim 1. There is no procedure given to determine the affinity of any substance to the receptors listed in claim 1. d) The nature of the invention is chemical synthesis, which involves chemical reactions. e) The state of the art for tumor binding agents is given in the references spanning line 22, page 13 to line 5, page 14. The state of the art is that even complete directions to a team of pharmacologist, enzymologists, and immunologists to search for radical "E", hardly constitute direct to the chemist of how to make these substances. f) The artisan using Applicants invention to prepare the compounds

whose use is claimed would be a process chemist or pilot plant operator with a BS degree in chemistry and several years of experience. g) Chemical reactions are well-known to be unpredictable, *In re Marzocchi*, 169 USPQ 367, *In re Fisher*, 166 USPQ 18. h) The breadth of the claims includes all the presently unknown list of functionally described radicals E embraced by claim 1. Reference AR teaches the use of an octapeptide which binds to the somatostatin receptor. A radical which derived from this peptide would fit the definition of "E" but is unclear if there additional such peptides or how the peptide Cytate was identified. The scope of the claimed subjected matter, as far as the "E" radical, is enormous.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

Applicants make no arguments concerning this rejection but simply assert that they are enabled for making all of these unknown molecules. How that is

possible when synthetic procedures the process chemist would need are left unsaid?

9. Claims 12-14 and 23-33 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way to convey reasonably to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The issues concerning the meaning of phrases "somatostatin receptor binding molecule" ... "carbohydrate receptor binding molecule" and "E is a target binding unit that is recognized by and binds to a target site on the tissue" are discussed above. Claims 12 and 32 do not contain a complete generic formula.

According to the MPEP §2163 I. A. "the issue of a lack of adequate written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant had possession of the claimed invention. The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art." The MPEP states in §2163 II 3 ii) "The written

description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see i)(A), above), reduction to drawings (see i)(B), above), or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.” Applicants have disclosed no species and have made no assertion that there is any correlation between the biological function of radical “E” and its structure.

As discussed above the phrase ““somatostatin receptor binding molecule” ... “carbohydrate receptor binding molecule” and “E is a target binding unit that is recognized by and binds to a target site on the tissue” are not art recognized in medicinal chemistry. According to the MPEP §2163.02 Standard for Determining Compliance With the Written Description Requirement,

“The courts have described the essential question to be addressed in a description requirement issue in a variety of ways. An objective standard for determining compliance with the written description requirement is, “does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed”. *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written

description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter". *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983))."

Thus, the chemist of ordinary skill in the art, who would make Applicants' compounds, would not know what "somatostatin receptor binding molecule" ... "carbohydrate receptor binding molecule" and "E is a target binding unit that is recognized by and binds to a target site on the tissue" were. That chemist would not have understood the inventor to be in possession of the claimed compounds at the time of filing.

This case was filed before Applicants had a clear idea of the structures of their desired compounds, how to make their compounds, and use them. The specification provides broad areas of future research and speculation, inviting undue experimentation in learning how to use Applicants' invention. Applicants may well now be developing practical applications of their photosensitizers, but the question here is what application they possessed at the time of filing. Anything is possible but as the U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences wrote in *Bindra v. Kelly*, 206 USPQ 570 "*Probable* utility does

not establish practical utility. Practical utility can, in our view, be established only by actual testing therefore, or by establishing such facts as would be convincing that such utility could be "foretold with certainty." *Blicke v. Treves*, supra, 112 USPQ at 475."


Applicants are reminded of what the U.S. Court of Appeals Federal Circuit wrote in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398, "In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus." "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See *Fiers*, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing Amgen). "It is only a definition of a useful result rather than a definition of what achieves that result." "The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.")".

Applicants rely upon the declaration by Dr. Rajajoplan under 37 CFR 1.132 filed 1/24/05 to overcome these rejections. That declaration is discussed above.

Conclusion

10. Information regarding the status of an application should be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free). Please direct general inquiries to the receptionist whose telephone number is (703) 308-1235.

11. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (571) 272-0670. The FAX number for amendments is (571) 273-8300. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 9:00am to 5:30pm, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, please contact James O. Wilson, acting SPE of Art Unit 1624, at (571)-272-0661.


Thomas C. McKenzie, Ph.D.
Primary Examiner
Art Unit 1624

TCMcK/me